Instruments of Science
An Historical Encyclopedia

Editors
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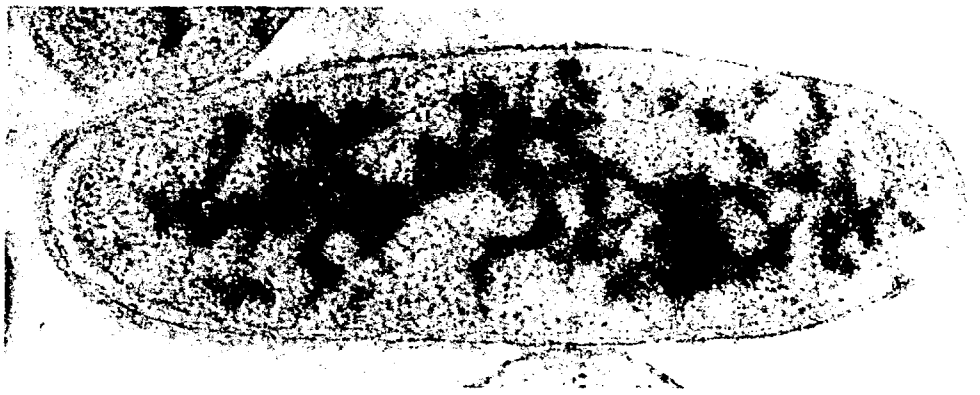

Electron micrograph of an ultrathin section of an E. coli *bacterium, showing DNA stained by an immunological procedure. Carl Robinow and Eduard Kellenberger, "The Bacterial Nucleoid Revisited."* Microbiological Reviews *58 (1994): 211-232, Figure 14(c). Courtesy of the American Society of Microbiology.*

Escherichia coli

E. (Escherichia) coli is a small bacterium universally found in the intestinal tract of birds and mammals, including humans. Most strains are part of the normal microflora of healthy individuals, and they probably play some beneficial role in crowding out other, pathogenic bacteria and in providing some traces of rare vitamins.

It may be curious to regard *E. coli* as an instrument. August Krogh had noted, in 1929, "For a large number of problems there will be some animal of choice, or a few such animals, on which it can be most conveniently studied." We do generalize from "animals" to organisms more broadly, from bacteria to yeast, maize, fruit flies, and mice, not to mention human cells for direct experimentation, and human individuals and populations for observation. Except for the difficulties in laboratory culture of many species, it may also be true that every organism is superbly suited to the study of some particular problem. For the difficult to culture, that is already the challenge.

E. coli has become the species of choice for a wide range of biological problems. In 1994, according to the database of the Institute for Scientific Information (ISI), 2,703 published articles included *E. coli* in their titles. This compares to 1,244 for *Drosophila,* 9,156 for the mouse, 1,575 for guinea pigs, but only 115 for *Shigella* and 619 for *Salmonella.* The latter two are related bacteria whose importance in disease far outweighs that of *E. coli.* The numbers for mice and guinea pigs reflect the widespread use of these animals for routine tests of toxicity of new drugs and other chemicals. All these numbers are underestimates by a factor of two or so, as the species name is not always given in the title. For mechanical or electrical instruments, it would be even more problematical how to estimate their importance by counting the literature. But for comparison, 1,733 articles had "mass-spec . . ." in their titles (*see spectrometer, mass*).

The name *Escherichia* honors Theodor Escherich, a German pediatrician who discovered and characterized "Bacterium coli" in 1885 as a common saprophyte in the human colon. It was renamed in 1919 in a revision of bacteriological nomenclature after the term "Bacterium" had become overloaded with too many diverse forms. *E. coli* thus dates to the very origins of modern bacteriology, most of which was preoccupied with dangerous pathogens like the "bacilli" for tuberculosis, pneumonia, cholera, and diphtheria. From the beginning, *E. coli* was used as a representative, harmless bacterium that could be safely and easily cultivated even on synthetic media. With its rapid growth, almost three doublings an hour, it forms readily visible colonies from single cells overnight on agar media. In liquid media, the cloudy growth is readily dispersed, so that single-cell colonies or clones are readily cultivated by simple plating procedures. It is also helpful that several chromogenic media have been devised (Eosin-Methylene Blue; X-gal; tetrazolium) that give vivid reports of various metabolic functions, reflected in colony pigmentation. During the first half of the twentieth century, *E. coli* was probably the single most studied bacterial species for basic physiological and metabolic investigation, but it was rarely mentioned in general biology texts.

The turning point of *E. coli*'s popularity came in the mid 1940s with a series of investigations on bacteriophages grown on *E. coli,* and the demonstration of a form of sexual genetic recombination in the same species. *E. coli* was chosen for these studies because of its favorable husbandry. Soon, the very accumulation of knowledge, mostly concentrated on a single strain, "K-12," made it more likely that it would be a prototype for still further studies. This strain was found to harbor a lysogenic bacteriophage, lambda, which has seeded a scientific industry of its own, and it is the seat of a number of plasmids—intracellular DNA particles transmitted by conjugation. The latter in turn provided the basis for gene-splicing, genetic engineering, and modern biotechnology.

Strain K-12 was isolated in 1922 from human feces and kept for many years as a stock strain in the bacteriology department at Stanford University. In the 1940s, Charles E. Clifton used it for studies of nitrogen metabolism, and his colleague Edward L. Tatum borrowed it initially as a source of the enzyme tryptophanase in his work on the biosynthesis of tryptophane from indole and serine. During many years of cultivation in the laboratory, the strain has lost many of its "Smooth" surface antigens, which is just as well, as it provides further assurance of its harmlessness to people. K-12 entered the domain of genetics with Tatum's pioneering studies on the production of nutritionally deficient mutants in 1944. That work attracted my own attention and led to a collaboration and discovery of sexual recombination in 1946. Since then, K-12 has been used by thousands of other investigators for innumerable genetic studies, and its genome has by now been almost completely mapped and much of its DNA sequenced. In retrospect, we know how lucky was the choice of strain K-12. With the methods used in 1946, only one *E. coli* strain in twenty, chosen at random, would have been successfully crossed.

Some of the most important of the scientific applications have been in the field of gene regulation, and the elaboration of the concept of the "operon," with work centered at the Pasteur Institute in Paris. The Nobel prizes earned by Francois Jacob and Jacques Monod are but two of the dozen that by my account are affiliated with *E. coli.* The operon is a cluster of DNA structures that are repressed or activated to regulate the activities of several genes downstream on the same DNA strand. Monod is attributed with the aphorism that "what is true for *E. coli* will be true for the elephant," and by implication the human. He had in mind particularly the theory of tissue differentiation in embryological development. This has proven to be somewhat overoptimistic, and it points to one of the limitations of *E. coli* (or other bacteria) as a model for general biology. The chromosome structure of *E. coli,* generally a simple circle, is far less convoluted than that of eukaryotic cells, which are complexed with histones and subject to several orders of folding to generate the compact visible chromosomes. This is in keeping with the modest genome size of bacteria, measured in millions of nucleotide units, compared with three billion for the human. Nor do bacteria show the complex patterns of differentiation characteristic of higher eukaryotes. A simple, unicellular eukaryote, yeast, has come a long way to filling in this instrumental gap, as is reflected in its 2,435 articles in the ISI database.

For many years, another serious limitation of *E. coli* was the difficulty of introducing extraneous DNA into its cells; this has now been overcome with tricks like electroporation (high-voltage zaps) and exposure to calcium phosphate gels.

What more could be asked of this instrument? I have four suggestions:

1. To isolate or select for still more rapid growth, perhaps at higher temperatures. However, *E. coli* may already be close to the theoretical limits set by the pace of biosynthetic machinery.
2. To excise extraneous segments of DNA and reduce its genome size by half or more, partly in the service of more rapid growth.
3. To enhance the efficiency of spontaneous uptake of DNA, to emulate, for example, *Acinetobacter.*
4. To introduce the capacity for durable spores, to assist in the long-term preservation of cultures—which now entails liquid nitrogen temperatures.

But it is doubtful if these advantages would be worth giving up any of the existing panoply, and especially the enormous backlog of knowledge represented in a literature that must now encompass perhaps fifty thousand publications. It may not be too fanciful to expect that these enhancements could be achieved with the continued reengineering of strain K-12 itself.

Joshua Lederberg

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